1α(OH)D5, is prima facie obvious because the references teach a generic group of vitamin D derivatives of which 1α(OH)D5 is a "specific species". In their response to the Final Office Action, Applicants rebutted the prima facie case of obviousness by providing evidence (in the form of a declaration by Dr. Robert Moriarty) that the claimed compound exhibits surprisingly low calcemic activity compared to its closest analogues, 1α(OH)D3 and 1α(OH)D4. In an advisory action mailed January 4, 2000 the Examiner stated that she was not persuaded because the declaration did not show a statistically significant difference between the prior art compounds and the claimed compound.

Applicants then submitted a Continued Prosecution Application. In the First Office Action in the CPA case (Paper 19), the Examiner appears to take the position that (1) the results shown in the Moriarty declaration are not unexpected or unobvious, and (2) even if they were unexpected, the declaration "is not commensurate with the scope of the claims."

These rejections are respectfully traversed. The following discussion and attached declaration by Dr. Samad Hedayat are provided for the Examiner's consideration.

I. <u>There is a statistically significant difference between the prior art compounds and the claimed compound.</u>

The Moriarty declaration submitted in the parent case describes studies conducted by Lunar Corporation of Madison, Wisconsin under the direction of Dr. Joyce Knutson. The results of the study show that the claimed compound, 1α(OH)D5, is considerably less calcemic than its closest known analogs, 1α(OH)D4, 1α(OH)D3 and 1α,25(OH)$_2$D$_3$. The attached declaration under 37 CFR § 1.132 by Dr. Samad Hedayat indicates that these differences are indeed statistically significant.

Paragraph 5 of the Hedayat declaration attests to the fact that at dose levels of 0.042 and 0.25 μg/kg/day, the difference in the mean serum calcium of rats given 1α(OH)D5 is statistically significantly less than that of rats given 1α(OH)D$_4$.

Paragraph 7 of the Hedayat declaration attests to the fact that at dose levels of 0.042 and 0.25 μg/kg/day, the difference in the mean serum calcium of rats given 1α(OH)D5 is statistically significantly less than that of rats given 1α,25(OH)$_2$D$_3$.

In summary, there is a statistically significant difference between the calcemic activity of the claimed compound and its closest analogues.

II. The study results provided in the Moriarty declaration are unexpected.

Applicants strongly disagree that the results of the calcemia study were not unexpected. The compound most closely related to 1α(OH)D5 structurally is 1α(OH)D_4. The difference in molecular structure between 1α(OH)D5 and 1α(OH)D4 is that 1α(OH)D5 has a C24 ethyl group whereas 1α(OH)D4 has a C24 methyl group. Yet Knutson U.S. Patent No. 5,488,120 ("1α-Hydroxy Vitamin D_4 and Novel Intermediates and Analogues") teaches that 1α(OH)D4 is useful for the treatment of disorders of calcium metabolism by increasing serum calcium (see Col. 6, lines 29-30). Such a result would lead one skilled in the art to expect 1α(OH)D5 to have a similar effect, whereas, surprisingly, it does not.

Because its most closely related analog exhibits high calcemic activity, it would not have been obvious to one skilled in the art at the time of the present application to attempt to synthesize 1α-hydroxyvitamin D_5 for possible use in treating mammary neoplasia. Yet, due to its surprisingly low calcemic activity, 1α-hydroxyvitamin D_5 can be administered at sufficiently high levels to act as an antiproliferative and cell differentiating substance when acting on mammary tumor cells without significantly affecting calcium metabolism. This surprising result has been the catalyst for further studies of 1α(OH)D5 by applicants.

The Examiner relies on U.S. Patent No. 5,763,429 as evidence

that the claimed compound's lower tendency to cause hypercalcemia and/or hypercalcuria is not unexpected. The passage relied upon by the Examiner includes the sentence "The 1α-hydroxyvitamin D compounds of formula (I) of the present invention are those that have effective antiproliferative and cell differentiation activity . . . but have a lower tendency or inability to cause the undesired side effects of hypercalcemia and/or hypercalcuria." This sentence does not teach that 1α(OH)D5 has a lower tendency or inability to cause hypercalcemia and/or hypercalcuria. Rather, the sentence merely limits Bishop's claimed method to one in which the compound used in the method has a lower tendency or inability to cause the undesired side effects of hypercalcemia and/or hypercalcuria. Significantly, the only suitable compounds Bishop names are those already known in the art, including 1α(OH)D_4 (Col. 3, lines 47-52). Had Bishop known of the substantially lower tendency of 1α(OH)D_5 to cause hypercalcemia and/or hypercalcuria, he would have undoubtedly mentioned it in his application. The fact is applicants were the first to synthesize 1α(OH)D_5 and the first to discover its surprisingly low calcemic activity.

III. <u>The Moriarty declaration is commensurate with the scope of the claims.</u>

In the First Office Action the Examiner states that "applicant [sic] has only shown a difference between 1α(OH)D_4 and 1α(OH)D5." This is incorrect. The declarations by Drs. Moriarty

and Hedayat show a statistically significant difference in the tendency to increase serum calcium not only between 1α(OH)D_4 and 1α(OH)D_5, but also between 1α,25(OH)$_2D_3$ and 1α(OH)D_5 and between 1α(OH)D_3 and 1α(OH)D_5. Applicants have met the burden of showing a surprisingly unexpected property of the claimed compound when compared directly to its closest analogues.

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In summary, 1α(OH)D5 exhibits a surprisingly lower tendency to increase serum calcium levels compared to the closest prior art analogue, 1α(OH)D4, as well as the somewhat less relevant analogues 1α,25(OH)$_2D_3$ and 1α(OH)D3. For the foregoing reasons, Applicants submit that Claims 1-6 and 10-19 are in condition for allowance. Applicants request an early and favorable ruling allowing same. The Examiner is invited to telephone applicant's undersigned attorney if any unresolved matters remain.

Respectfully submitted,

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